ORGANIC LETTERS

2012
Vol. 14, No. 8
2022–2025

Design and Application of New Imidazolylsulfonate-Based Benzyne Precursor: An Efficient Triflate Alternative

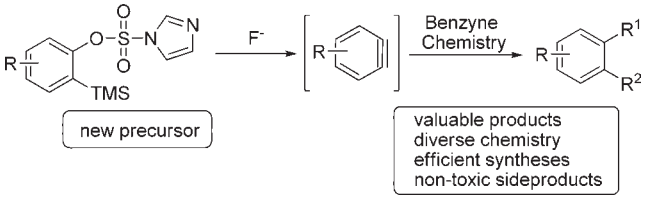
Szabolcs Kovács,[†] Ádám I. Csincsi,[†] Tibor Zs. Nagy,[†] Sándor Boros,[‡] Géza Timári,[‡] and Zoltán Novák*,[†]

Institute of Chemistry, Eötvös Loránd University, Pázmány Péter stny 1/a, H-1117 Budapest, Hungary, and Sanofi, Chinoin Zrt, Tó utca 1-4, H-1045 Budapest, Hungary

novakz@elte.hu

Received March 1, 2012

ABSTRACT



Several *o*-(trimethylsilyl)aryl imidazolylsulfonates were synthesized in a simple process and successfully applied in cycloadditions involving benzyne intermediates. The precursor offers an efficient alternative for generating benzynes compared to widely used ortho TMS triflates under similar reaction conditions. With the utilization of this new precursor, the formation of potentially genotoxic trifluoromethanesulfonate side product is eliminated. The applicability of the new benzyne precursor was demonstrated in different types of cycloaddition reactions to prepare heterocyclic molecules.

Arynes are reactive intermediates due to their strained structures caused by the presence of a distorted triple bond in the six-membered carbacycle.[1] This exotic compound class can be transformed efficiently in nucleophilic or electrophilic reactions,[2] in pericyclic reactions,[3] and in transition-metal-catalyzed reactions.[4] The power of aryne chemistry has been demonstrated in numerous natural product syntheses.[5] Generation of *o*-arynes requires two eliminable functional groups, which are in ortho positions to each other. Several aryne precursors have been used for the generation of the reactive intermediate including diazonium carboxylates,[6] iodonium triflates,[7] benzotriazole,[8] halotriflates,[9] fluorolithium, and magnesium compounds,[1a] but the most frequently used aryne precursor is 2-(trimethylsilyl)phenyl triflate. With the aid of Kobayashi's method, benzynes can be generated in a straightforward manner in a fluoride-induced reaction under mild reaction conditions.[10]

[†] Eötvös Loránd University.
[‡] Sanofi.

(1) For reviews, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Hart, H. In *The Chemistry of Triple-Bonded Functional Groups, Supplement C2*; Patai, S., Ed.; Wiley: Chichester, U.K., 1994; Chapter 18. (c) Gilchrist, T. L. In *The Chemistry of Functional Groups, Supplement C2*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1983; Chapter 11. (d) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (e) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (f) Bhunia, A.; Yetra, R. S.; Biju, T. A. *Chem. Soc. Rev.* **2012**, *41*, 3140–3152.

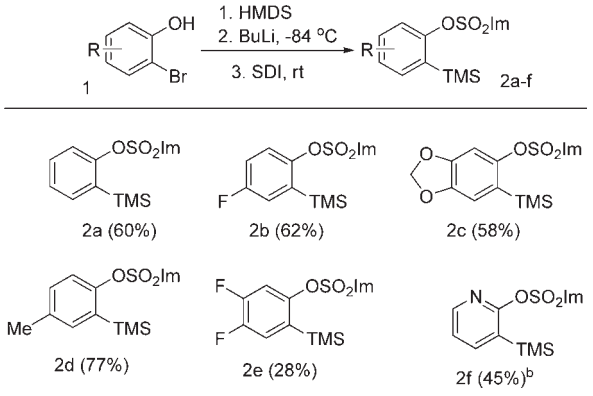
(2) (a) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247–3249. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341. (c) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113. (d) Łaczkowski, K. Z.; Garcia, D.; Peña, D.; Cobas, A.; Perez, D.; Guitian, E. *Org. Lett.* **2011**, *13*, 960–963. (e) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673–4675. (f) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99–102. (g) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007–1010. (h) McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667–3669. (i) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169–171. (j) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029–1032. (k) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761–9764. (l) Rémond, E.; Tessier, A.; Leroux, F. R.; Bayardon, J.; Jugé, S. *Org. Lett.* **2010**, *12*, 1568–1571. (m) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956–1959. (n) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168–171. (o) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117–3119. (p) Chai, G.; Qiu, Y.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 5196–5199. (q) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946–4949. (r) Alajarin, M.; Lopez-Leonardo, C.; Raja, R.; Orenes, R. *Org. Lett.* **2011**, *13*, 5668–5671. (s) Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845–3847. (t) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367–3370. (u) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int.Ed.* **2011**, *50*, 4488–4491. (v) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638–6642. (w) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559. (x) Hong, D.; Chen, Z.; Lin, X.; Wang, Y. *Org. Lett.* **2010**, *12*, 4608–4611. (y) Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525–1528.

10.1021/ol300529j
Published on Web 04/11/2012

However, the trifluoromethansulfonate functional group is an excellent leaving group for aryne generation, but the instability of triflates, the high cost of triflating agents, and the formation potentially genotoxic triflic acid appear as significant drawbacks in industrial applications. To circumvent these problems Albaneze-Walker introduced imidazolylsulfonates as a triflate alternative for Suzuki coupling.[11] The stable arylimidazolylsulfonates are easily prepared and straightforwardly transformed in the palladium-catalyzed coupling. In addition, the formed imidazole-sulfonic acid hydrolyzes during the workup to produce imidazole and sulfuric acid instead of toxic trifluoromethane-sulfonic acid.

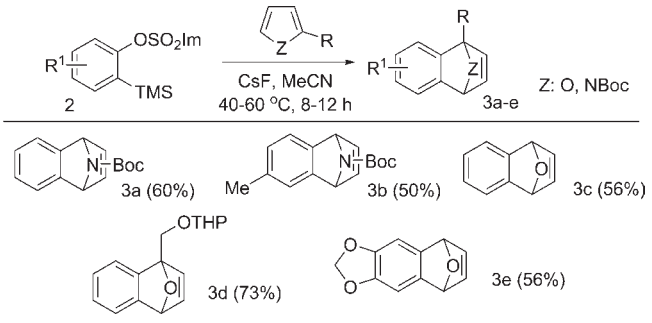
To exploit the advantages of imidazolylsulfonates over triflates, we aimed to design a new benzyne precursor family for organic syntheses. In the first step of the synthesis, *o*-bromophenols were silylated with HMDS to get TMS-protected bromophenols. After lithiation with BuLi, the formed *o*-silyl lithium phenolate intermediate can be reacted with sulfonyldiimidazole to obtain the new benzyne precursor (**2**). Through the three-step synthesis, the target compounds can be prepared without purification and isolation of any intermediates.

Scheme 1. Synthesis of New Imidazolylsulfonate-Based Benzyne Precursors[a]



[a] Key: (1) *o*-bromophenol derivative (5 mmol), HMDS (15 mmol), THF, 70 °C; (2) nBuLi (5 mmol), THF, −84 °C; (3) SDI (7.5 mmol), rt; (b) synthesis of **2f**: 2-hydroxy-3-trimethylsilylpyridine (0.6 mmol), SDI (0.9 mmol), Cs_2CO_3 (0.3 mmol) in THF at rt.

Scheme 2. Pericyclic Reactions of Sulfonylimidazolyl-Based Benzyne Precursor with Heterocyclic Dienes[a−c]



[a] Reaction with furan: aryne precursor (0.5 mmol), furan (0.8 mmol), CsF (1 mmol), MeCN, 40 °C. [b] Reaction with *N*-Boc-pyrrole: aryne precursor (0.5 mmol), *N*-Boc-pyrrole (1 mmol), CsF (1 mmol), MeCN, 60 °C. [c] Key: aryne precursor (0.8 mmol), 2-(furan-2-ylmethoxy)tetrahydro-2*H*-pyran (0.4 mmol), CsF (1.6 mmol), MeCN, 40 °C.

(3) (a) Xie, C.; Zhang, Y. *Org. Lett.* **2007**, *9*, 781–784. (b) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135–4137. (c) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96–99. (d) Ikawa, T.; Takagi, A.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Kakiguchi, K.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5563–5566. (e) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6842–6844. (f) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666–3669. (g) Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* **2011**, *13*, 2552–2555. (h) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323–3325. (i) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412. (j) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587–1590. (k) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180–1183. (l) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368–3371. (m) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234–2237. (n) Candito, D. A.; Panteleev, J.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14200–14203. (o) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199–5202. (p) Li, P.; Zhao, J.; Wu, C.; Larock, R. C. *Org. Lett.* **2011**, *13*, 3340–3343.

(4) (a) Caeiro, J.; Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Adv. Synth. Catal.* **2006**, *348*, 2466–2474. (b) Sato, Y.; Tamura, T.; Kinbara, A.; Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 647–661. (c) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Huang, X.-C.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 3199–3202. (d) Worlikar, S. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2413–2416. (e) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716–15717. (f) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 391–394. (g) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589–5592. (h) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535–2538. (i) Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309–2312. (j) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572–577. (k) Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2006**, *8*, 5057–5060. (l) Worlikar, S. A.; Larock, R. C. *Curr. Org. Chem.* **2011**, *15*, 3214–3232.

(5) (a) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**10.1002/anie.201107485. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**10.1021/cr200478h. (c) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629–8630. (d) Gillespie, J. P.; Amros, L. G.; Stermitz, F. R. *J. Org. Chem.* **1974**, *39*, 3239–3241. (e) Ilda, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc. Perkin Trans. 1* **1975**, 2502–2566. (f) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888. (g) Watanabe, M.; Kurosaki, A.; Furukawa, S. *Chem. Pharm. Bull.* **1984**, *32*, 1264–1267. (h) Atanes, N.; Castedo, L.; Guitian, E.; Saa, C.; Saa, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984–2988. (i) Perez, D.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5911–5917. (j) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568–3570. (k) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525. (l) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214–3222. (m) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752–11753. (n) Soorukram, D.; Qu, T.; Barrett, A. G. M. *Org. Lett.* **2008**, *10*, 3833–3835. (o) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270–17271. (p) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201–204. (q) Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1612–1614.

(6) (a) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1549–1550. (b) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Org. Synth.* **1968**, *48*, 12–17. (c) For a mechanistic study, see: Buxton, P. C.; Fensome, M.; Heaney, H.; Mason, K. G. *Tetrahedron* **1995**, *51*, 2959–2968.

(7) Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983–984.

(8) Campbell, C. D.; Rees, J. *J. Chem. Soc.* **1969**, 742–747.

(9) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736.

(10) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.

Utilizing the procedure, we prepared six different precursors (Scheme 1) including the basic compound (**2a**) and mono (**2b**) and difluoro (**2e**) derivatives. Molecules with electron-donating methyl (**2d**) or 1,3 dioxolyl groups (**2c**) was also prepared in good yield considering the three-step synthesis. A heterocyclic precursor such as 3-(trimethylsilyl)-pyridin-2-yl imidazolsulfonate (**2f**) was synthesized from 2-hydroxy-3-trimethylsilylpyridine and sulfonyldiimidazole in the presence of Cs_2CO_3.

With diverse imidazolylsulfonate-based precursors in hand, we aimed to demonstrate their applicability in different types of cycloaddition reactions where benzynes are key intermediates.[12]

First, to prove the applicability of the new precursor in benzyne chemistry, we performed several cycloadditions with dienes such as furans and *N*-Boc-pyrrole (Scheme 2). To our delight, we proved the formation of the benzyne with successful trapping of this reactive intermediate with both heterocyclic dienes in pericyclic reaction. Reaction of Boc-pyrrole afforded the appropriate cycloadduct (**3a**) with 60% yield. Reaction with the methyl-substituted precursor gave a similar result, and product **3b** was obtained with 50% yield. Reaction of furans gave results similar to those obtained with pyrroles, and we obtained the bridged heterocycles **3c**–**e** bearing substituents delivered either by the precursor or the furan.

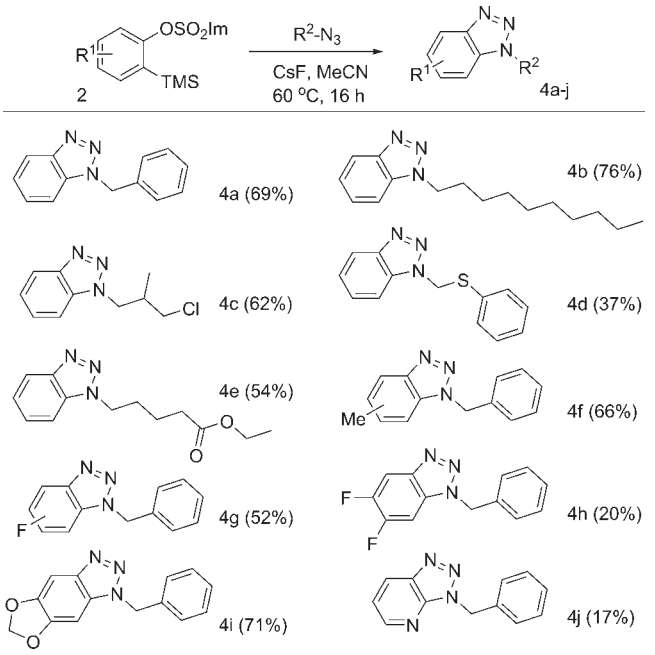
After the first successful demonstration of the applicability of our new precursor in benzyne chemistry, we sought current synthetic transformations in which *o*-trimethylsilyl triflates are used as precursors.

A cycloaddition reaction of benzynes with azides gave benzotriazoles in a straightforward manner as described by Larock and co-workers.[3i] First, the unsubstituted sulfonylimidazolyl (**2a**) precursor was reacted with several azides in MeCN at 60 °C. As expected, the appropriate benzotriazole products were isolated with 37–76% yield depending on the functional groups attached to nitrogen atom of the benztriazol ring.

N-Benzyl-substituted benzotriazole (**4a**) was synthesized with 69% yield, while the presence of a long alkyl chain increased the yield of the appropriate product (**4b**) (Scheme 3). The cycloaddition can be achieved successfully also with other alkyl azides bearing chloride and ester functional groups (**4c**, **4e**).

Only the thioether (**4d**) was obtained in moderate yield. Precursors with fluoro or methyl functionality gave regioisomeric mixtures of 5- and 6-substituted benzotriazoles **4f** and **4g** in 1:1 and 7:3 ratios, respectively.[13] Electron-rich disubstituted precursor **2c** provided a better yield of the appropriate benzotriazole (**4i**) than **2e** bearing two fluoride groups. Reaction of benzyl azide and heterocyclic

Scheme 3. Synthesis of Benzotriazoles[a]



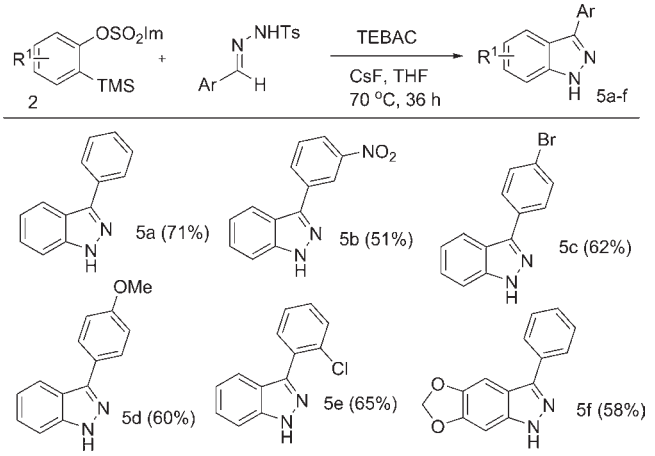
[a] Key: aryne precursor (0.34 mmol), azide (1.02 mmol), CsF (1.02 mmol), MeCN, 60 °C.

3-(trimethylsilyl)pyridin-2-yl imidazolylsulfonate (**2f**) gave 3-benzyltriazolopyridine (**4j**) regioselectively.

To compare the reactivity of 2-(trimethylsilyl)phenyl triflate and imidazolylsulfonate in this cycloaddition, we monitored their reactions with benzyl azide. The comparative studies showed that both precursors had similar reactivity under the applied conditions.[14]

We continued our investigations into the formation of 3-aryl-substituted indazoles as an important heterocyclic compound family to demonstrate the synthetic applicability of our benzyne precursor.

Scheme 4. Synthesis of Indazoles[a]



[a] Key: tosylhydrazone (0.4 mmol), aryne precursor (0.48 mmol), TEBAC (0.1 mmol), CsF (1.2 mmol), THF, 70 °C.

(11) Albaneze-Walker, J.; Raju, R.; Vance, A. J.; Goodman, J. A.; Reeder, R. M.; Liao, J.; Maust, T. M.; Irish, A. P.; Espino, P.; Andrews, R. D. *Org. Lett.* **2009**, *11*, 1463–1466.

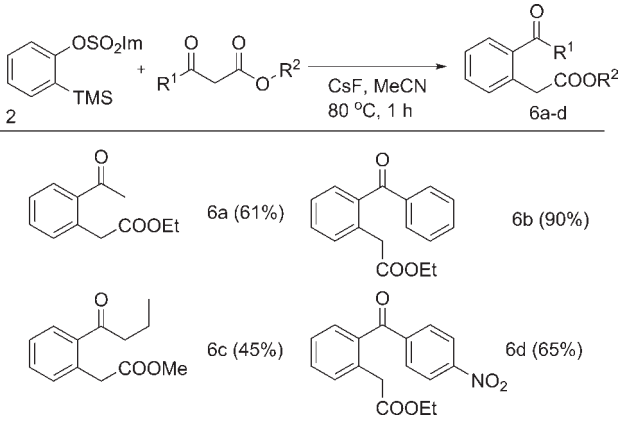
(12) Besides cyloaddition, we reacted the benzyne precursor **2a** with phenol as a simple nucleophile, and diphenyl ether was isolated in 79% yield after the reaction.

(13) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.

Applying Larock's conditions[3p] for the reaction of trimethylsilyl imidazolesulfonates with *N*-tosylhydrazones, we were able to prepare several indazoles bearing electron-withdrawing and electron-donating substituents on the phenyl ring in position 3 (Scheme 4, **5a**–**e**). The presence of a 1,3-dioxolyl group in the benzyne precursor did not affect the reaction, and the appropriate indazole was obtained with a yield similar to obtained for the unsubstituted derivative.

As described by Tambar and Stoltz, *o*-acyl alkylation of the aromatic ring takes place straightforwardly when benzyne is generated from *o*-silyl-aryltriflates in the presence of *β*-ketoesters.[2b]

Scheme 5. Acyl Alkylation of Benzyne[a]



[a] Key: aryne precursor (0.5 mmol), *β*-ketoester derivative (0.4 mmol) and CsF (1 mmol) were stirred in MeCN at 80 °C.

Adopting the conditions of Stoltz, we prepared several compounds from our sulfonylimidazolyl-based precursor. All the representative reactions gave the appropriate acylalkylated product with good to excellent yield (Scheme 5, **6a**–**d**).

Summarizing our results, we designed and developed a new benzyne precursor family as a good alternative for *o*-silyl phenyltriflate due to its stability and easy handling properties. The sulfonylimidazol based precursors were conveniently prepared from *o*-bromophenols in a simple multistep procedure without the isolation of any intermediate. The formation of imidazolesulfonic acid in the reaction eliminates the problems of potentially genotoxic trifluoromethyl sulfonates because of its hydrolytic cleavage to imidazole and sulfuric acid after aqueous workup. We demonstrated that the sulfonylimidazole-based benzyne precursors could be successfully utilized in several transformations, and their observed reactivity offers a good alternative for benzyne generation in addition to the widely used *o*-trimethylsilylaryl triflates.

Acknowledgment. We thank Sanofi for the generous research support and Graduate Scholarship for Sz.K. The aid of Prof K. Torkos (Eötvös Loránd University, Institute of Chemistry) and Dr. Zs. Eke (Eötvös Loránd University, Institute of Chemistry) in providing the necessary analytical background is gratefully acknowledged. This work was supported by OTKA-NKTH (CK 80763). The European Union and the European Social Fund have provided financial support to the project under Grant Agreement No. TÁMOP 4.2.1./B-09/KMR-2010-0003.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) For further details, see the Supporting Information.

The authors declare no competing financial interest.